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REVIEW

Microglial polarization: novel therapeutic mechanism against Alzheimer's disease

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Abstract

Alzheimer's disease (AD) is the most prevalent neurodegenerative disease that results in progressive dementia, and exhibits high disability and fatality rates. Recent evidence has demonstrated that neuroinflammation is critical in the pathophysiological processes of AD, which is characterized by the activation of microglia and astrocytes. Under different stimuli, microglia are usually activated into two polarized states, termed the classical 'M1' phenotype and the alternative 'M2' phenotype. M1 microglia are considered to promote inflammatory injury in AD; in contrast, M2 microglia exert neuroprotective effects. Imbalanced microglial polarization, in the form of excessive activation of M1 microglia and dysfunction of M2 microglia, markedly promotes the development of AD. Furthermore, an increasing number of studies have shown that the transition of microglia from the M1 to M2 phenotype could potently alleviate pathological damage in AD. Hence, this article reviews the current knowledge regarding the role of microglial M1/M2 polarization in the pathophysiology of AD. In addition, we summarize several approaches that protect against AD by altering the polarization states of microglia. This review aims to contribute to a better understanding of the pathogenesis of AD and, moreover, to explore the potential of novel drugs for the treatment of AD in the future.

Keywords Alzheimer's disease · Microglia · Inflammation · Inflammatory signalling pathway · NF-κB

Introduction

Alzheimer's disease (AD) is a multifactorial neurodegenerative disease that is caused by genetic and non-inheritable components. Most cases are sporadic, as only 5–20% of AD cases have familial history. Intracellular neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau and extracellular deposits of amyloid β (Aβ) are considered to be the two key hallmarks of AD. Importantly, more and more evidence has demonstrated that neuroinflammation is also a crucial player in the onset and development of AD, which is characterized by astrocytic and microglial activation. Excessive neuroinflammation promotes the generation of inflammatory mediators such as cytokines and chemokines, which results in neuronal injury and neurodegeneration. A noticeable neuroinflammatory response has been detected in both sporadic and familial AD, as well as in transgenic models of the disease (Akiyama et al. 2000). In vivo studies have shown that Aβ treatment activates microglia and aggravates inflammatory responses by binding to innate immune receptors on microglia (Stewart et al. 2010; Liu et al. 2012a, b; Wirz 2013). Taken together, these observations have formed the inflammatory cascade hypothesis of Alzheimer's disease.

In addition to being crucial cellular mediators of neuroinflammatory processes, microglia play a vital role in overall brain maintenance, and participate in inflammatory and immune responses in the central nervous system (CNS) (Lawson et al. 1992; Gehrmann et al. 1995). Microglia display neurotoxic or neuroprotective functions in the CNS depending upon the phenotypic polarization, thereby acting as a 'double-edged sword'. Microglia are usually activated into two polarized states, termed the classical 'M1' phenotype and the alternative 'M2' phenotype. M1 microglia are considered to enhance pro-inflammatory responses by secreting large numbers of inflammatory cytokines that lead to tissue damage (Orihuela et al. 2016). In contrast, M2 microglia exert neuroprotective effects by inhibiting

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neuroinflammation, thereby promoting tissue repair (Mantovani et al. 2004; Edwards et al. 2006).

In the early stage of AD, even before the formation of senile plaques, activated microglia exert protective effects by reducing Aβ deposition (Solito and Sastre 2012), alleviating tau hyperphosphorylation (Jiang et al. 2016) and secreting neurotrophic factors (Fillit et al. 1991). However, during the development of AD, the excessive activation of microglia promotes inflammatory injury and aggravates AD-related pathological damage (Mcdonald et al. 1997; Lue et al. 2010). Recent studies have revealed that microglial polarization may be a promising therapeutic target in AD. In both in vivo study and in vitro studies, experimentally inducing microglial polarization towards the neuroprotective M2 phenotype, has been shown to significantly alleviate neuroinflammatory responses and ameliorate pathological damage in AD models (Jiang et al. 2016; Oh et al. 2017; Yu et al. 2017; Zhang et al. 2017). Nevertheless, the regulatory mechanisms involved in microglial polarization are not well known. Hence, the current article aims to review the role of microglial polarization in AD, and to summarize potential microglial-based therapeutic targets for treating AD.

Microglia in the CNS

The micro-environment of the CNS is mainly composed of neurons and glial cells, the latter of which includes microglial cells, astrocytes and oligodendrocytes. Derived from embryonic mesodermal-marrow precursor cells, microglia provide potent neurotrophic and neuroprotective effects in the CNS (Hume et al. 2002). Additionally, as the major immunological effector cells in the CNS, microglia exhibit scavenger-like immune activity in terms of inflammatory and immune responses. Under physiologically healthy conditions, microglia have small cell bodies, slender branching, and do not engage in phagocytosis (Nimmerjahn et al. 2005). Under several pathological conditions, activated microglia are rapidly converted into an amoeba-like large morphology, engage in synaptic pruning and migrate to the lesion region to provide strong phagocytic activities (Nakamura et al. 1999). Consequently, abundant pro-inflammatory cytokines such as tumour necrosis factor-α (TNF-α), interferon γ (IFN-γ) and interleukin-1 (IL-1) are generated, and lead to neuroinflammatory responses.

Microglia act like a 'double-edged' sword to provide beneficial or harmful effects in the CNS, depending on the phenotypic polarization. Microglia are usually activated into two polarized states, termed the classical 'M1' phenotype and the alternative 'M2' phenotype. The M1 phenotype is induced by immune stimulation such as from lipopolysaccharides (LPSs) and INF-γ, which induces microglia to secrete large amounts of pro-inflammatory factors including nitric oxide (NO), TNF-α, IL-6 and IL-lβ (Ponomarev et al. 2007; Orihuela et al. 2016). Hence, the classic activation state of the M1 phenotype promotes neuroinflammatory responses. In contrast, in response to inflammatory stimuli such as IL-4 and IL-13, microglia are converted into the M2 phenotype (Tang and Le, 2016). M2 microglia display beneficial effects by releasing neuroprotective cytokines such as IL-10, transforming growth factor-β (TGF-β) and insulin-like growth factor 1 (IGF-1). Additionally, the alternative activation state of the M2 phenotype inhibits excessive neuroinflammation induced by M1 microglia, which leads to tissue repair and reestablishment (Mosser 2003; Mantovani et al. 2004; Edwards et al. 2006; Mosser and Edwards 2008). During the clearance of apoptotic cells or myelin fragments by M2 microglia, M2 markers such as arginase-1 (Arg1) and mannose receptor (CD206) are generated to aid in tissue reconstruction and synaptic remodelling (Boche et al. 2006; Suh et al. 2013). M2 activation is divided into additional sub-categories. Accompanied by different markers, the expressions of mannose receptor (MRC1) and Arg1 are considered to be indicative of M2a activation. In contrast, elevated expressions of CD86 and the major histocompatibility complex II (MHCII) receptor are consistently observed during $M2_b$ activation. Finally, the M2c phenotype is characterized by amplified expressions of transforming growth factor β1 (TGFβ1) and sphingosine kinase 1 (SPHK1) (Mosser 2003; Mosser and Edwards 2008). Despite these established subclassifications, the functions of M2 microglia sub-phenotypes are not well understood and require future investigations for their further elucidation.

Microglia in AD

Depending on the polarized state, microglia manifest dual toxic and protective roles in the process of AD. Previous studies have shown that moderate microglial activation alleviates AD pathological damage and reduces Aβ levels via phagocytosis and induction of tissue repair. However, excessive neuroinflammation releases toxins such as nitric oxide (NO) and pro-inflammatory cytokines/chemokines, which exacerbates neuronal injury and, consequently, accelerates AD progression (Michaud et al. 2013).

Toxic function of microglia in AD

It has been reported that excessive activation of M1 microglia aggravates the pathological damage in AD via multiple mechanisms. First, M1 microglia promote the production of large amounts of pro-inflammatory cytokines such as TNF-α, IL-1 and macrophage inflammatory protein-1 (MIP-1) that consequently exacerbate neuronal damage, Aβ deposition (Mcdonald et al. 1997; Lue et al. 2010; Krabbe et al. 2013) and cholinergic neuronal injury (Raleigh 2006; Wyss-Coray 2006). Second, aggregation of activated microglia has

been shown to surround NFTs at both early and late stages of AD (Sheng et al. 1997; Sheffield et al. 2000). The inflammatory cytokines secreted by M1 microglia such as IL-1, IL-6 and fractalkine (CX3CL1) modulate the structure and function of tau, moreover, promote tau hyperphosphorylation and formation of NFTs (Bhaskar et al. 2010). In addition, during the progression of AD, the persistent activation of M1 microglia releases many neurotoxic substances, such as pyridinedicarboxylic acid and amines, that result in neuronal excitotoxicity (Giulian et al. 1995; Leipnitz et al. 2007). Furthermore, more and more evidence has suggested that microglial phagocytosis of Aβ is significantly inhibited during AD because of diminished expression of specific proteins in microglia/macrophages, including scavenger receptor (SR-A), receptor for advanced end glycation products (RAGE) and insulin degrading enzyme (IDE) (Koenigsknechttalboo and Landreth 2005). Other M1 microglia-mediated pro-inflammatory cytokines, such as IFN-γ and TNFα, not only inhibit uptake of Aβ, but also block internalized Aβ degradation (Yamamoto et al. 2008; Michelucci 2009). Interestingly, recent studies have found that excessive M1 microglial activation facilitates the spread of Aβ and tau. Venegas et al. (2017) found that apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC) specks is released by microglia. ASC specks promote the production of Aβ oligomers and Aβ aggregation, and injection of ASC specks into hippocampus aggravates the spread of Aβ in different brain regions in APPSwePSEN1dE9 mice, which is considered to be a key hallmark of AD progression. Another study used an adeno-associated virus-based model that exhibited rapid tau propagation from the entorhinal cortex to the dentate gyrus within 4 weeks. The results of this study showed that depleting microglia markedly prevented the propagation of tau and reduced tau spreading from the entorhinal cortex to the hippocampal region, indicated that microglia exacerbated tau spreading via exosome secretion (Asai et al. 2015).

Neuroprotective function of microglia in AD

The alleviated scavenging activity of Aβ has been reported to be the main reason for the progression of pathology in the majority of sporadic AD cases (Sollvander et al. 2016). In the early stage of AD, even before the formation of senile plaques, activated microglia exert protective effects in Aβ deposition by phagocytosis and releasing Aβ-degrading enzymes (Solito and Sastre 2012). Pro-inflammatory M1 microglia appear to be impaired in their ability to clear Aβ; in contrast, M2 microglia have been shown to be efficient phagocytes. Many studies have shown that Aβ activates microglia and neuroinflammation in the CNS (D'Andrea et al. 2004; Liu et al. 2018), and that misfolding and aggregated Aβ protein can be phagocytosed and cleared by activated microglia. Scavenger receptors are a group of evolutionally conserved proteins that are expressed on the surface of microglia and act as receptors for Aβ. SCARA-1 (scavenger receptor A-1), CD36 and RAGE are some examples of scavenger receptors (Wilkinson and El 2012). Simulating M2 activation with cytokine IL-4 and IL-10 effectively blocks lipopolysaccharide-induced inhibition of Aβ phagocytosis (Koenigsknechttalboo and Landreth 2005; Michelucci, 2009; Kawahara et al. 2012). Treatment with IL-4, a strong inducer of M2 polarization, facilitates the degradation of internalized Aβ by phagosomes and lysosomes (Majumdar et al. 2007; Balce et al. 2011). Different subtypes of M2 microglia have been shown to exhibit unique functions. IL-4-induced M2a microglia have significant Aβ scavenging activity, while M2c microglia—induced by IL-10, TGFβ1 and glucocorticoids—may play a crucial role in tissue repair (Mecha et al. 2015). Additionally, a previous study demonstrated that M2 microglial products prevented inter-neuronal transfer of Aβ and reduced the spread of Aβ in the AD brain (Sackmann et al. 2017). Furthermore, M2 microglia markedly alleviate neuroinflammatory responses and prevent tau hyperphosphorylation, which ameliorates pathological damage in AD (Jiang et al. 2016). Additionally, M2 microglia provide neuroprotective effects by releasing anti-inflammatory cytokines such as IL-10 and TGF-β (Colton 2009), and secreting neurotrophic factors such as nerve growth factor (NGF). M2 microglia also potently suppress the generation of neuronal toxins (e.g., glutamic acid), which promotes tissue repair and synaptic regeneration (Fillit et al. 1991; Lambeth 2004; Gandy and Heppner 2013).

Microglia-based therapy in AD

It has been reported that inhibitors of excessive neuroinflammatory responses alleviate pathological damage in AD. In vitro studies have shown that non-selective inhibitors of cyclooxygenase (COX) can preferentially decrease the levels of the highly amyloidogenic $A\beta_{1-42}$ peptide. In murine models of AD, similarly, non-selective NSAIDs reduce Aβ plaque deposition in the brains of rodents (Pasinetti 2002). A prospective study demonstrated that the long-term use of NSAIDs might protect against AD, but not against vascular dementia (In et al. 2001). Other inflammatory regulators have also been shown to provide neuroprotective functions in AD, such as phosphodiesterases (PDEs) (Zhang et al. 2013; Guo et al. 2017a, b), histone deacetylase (Ke et al. 2011) and NADPH oxidase (NOX) (Laibaik et al. 2008). These controversial results were provided by the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT). The authors found that anti-inflammatory drugs (i.e., naproxen and celecoxib) delayed cognitive decline in slow decliners while accelerating decline in fast decliners (Ji et al. 2018). Besides, more and more evidence has revealed

that modulators of microglial phenotypes may be a promising therapeutic approach for the treatment of AD.

AMPK-signalling agonists

AMP-activated protein kinase (AMPK) plays a crucial role in mitochondrial biogenesis, lipid metabolism and inflammation (Giri et al. 2004). AMPK signalling is activated in response to stresses that deplete cellular ATP supplies, such as low glucose, hypoxia and ischemia. Moreover, AMPK signalling can be activated by upstream AMPK kinases, such as LKB1 and calmodulin-dependent protein kinase β (CaMKKβ). Recent evidence has demonstrated that AMPK signalling is involved in microglial polarization. For instance, peroxisome proliferator-activated receptor γ (PPARγ), a ligand-activated transcription factor, regulates microglial polarization and inflammatory responses, as well as glucose and lipid metabolism (Zhao et al. 2016; Ji et al. 2018). Many studies have revealed that treatment with PPARγ agonists reduces CNS Aβ levels and alleviates AD pathology (Escribano et al. 2010; Mandrekarcolucci et al. 2012; Yamanaka et al. 2012). Additionally, PPARγ agonists have been considered to efficiently provide neuroprotective properties via increasing mRNA levels of the M2 marker, YM1 (Mandrekarcolucci et al. 2012), as well as the scavenger receptor, CD36 (Yamanaka et al. 2012). The modulatory effect of PPARγ in microglial polarization might be due to the activation of the LKB1–AMPK signalling pathway (Ji et al. 2018). Furthermore, the LKB1 inhibitor, radicicol, or knockdown of LKB1 prevented AMPK-signalling activation and the T0070907-induced M1-to-M2 phenotypic shift in LPS-treated BV2 microglial cells (Ji et al. 2018). Another study explored the effects of the CaMKKβ inhibitor, STO-609, and CaMKKβ siRNA. The results demonstrated that CaMKKβ promoted downstream betulinic acid (BA)-mediated AMPK activation and microglial M2 polarization. Pre-administration of the AMPK inhibitor blocked M2 microglial polarization in the cerebral cortex of LPS-injected mice brains (Li et al. 2018). In addition, telmisartan, an angiotensin II type 1 receptor blocker, promoted cerebral AMPK activation and M2 microglial gene expression in a mouse model of LPS-induced neuroinflammation (Xu et al. 2015). Taken together, AMPK-signalling agonists have potential positive effects in the regulation of microglial polarization and neuroinflammatory responses, which may represent promising therapeutic approach in AD.

mTOR-signalling inhibitors

As a self-digestion process, cell autophagy degrades useless proteins and organelles through the autophagy–lysosome pathway. Numerous studies have revealed that moderate autophagy exerts protective effects in several neurodegenerative diseases, including AD. However, excessive and uncontrolled autophagy leads to cellular injury and promotes the development of disease (Zare-Shahabadi et al. 2015). As a vital regulatory signalling pathway in cellular autophagy, the mechanistic target of rapamycin (mTOR) pathway inhibits autophagy when activated by upstream kinases such as AKT and MAPK. Recent studies have indicated that mTOR pathway inhibitors promote M2 macrophage polarization (Saxton and Sabatini 2017). Zhu et al. (2014) found that tuberous sclerosis complex 1 (TSC1) facilitated M2 properties by mTOR-dependent CCAAT/enhancer-binding protein-β pathways, and also showed that mTOR inhibition promoted M1 to M2 macrophage polarization. In a model of spinal cord injury (SCI) and in an LPS-treated BV-2 cell model, salidroside (Sal) pre-treatment significantly induced M2 microglia activation and M1 polarization inactivation via enhanced AMPK phosphorylation and reduced mTOR phosphorylation; this effect was reversed by CQ, a specific lysosome inhibitor, that is commonly used to block autophagic flux (Wang et al. 2017). In a model of vascular dementia, paeoniflorin (PF), a cannabinoid receptor 2 (CB2R) agonist, facilitated an M1 to M2 phenotypic transition in microglia/macrophages in the hippocampus of rats; this manipulation consequently improved animal learning and memory. Moreover, PF treatment significantly inhibited the mTOR/NF-κB pro-inflammatory pathway and enhanced the PI3K/Akt anti-inflammatory pathway (Luo et al. 2018). Similarly, the mTOR inhibitor, everolimus (RAD001), inhibited mTORC1 activity and ameliorated VaD by promoting the M1 to M2 microglial shift (Huang et al. 2017). In a mouse model of traumatic brain injury (TBI), Huang et al. (2017) found that miR-124-3p promoted the generation of anti-inflammatory M2 microglia and blocked neuronal inflammation by inhibiting mTOR signalling. Additionally, by crossing Raptor loxed ($Raptor^{flox/flox}$) mice with $CX3CR1^{CreER}$ mice, blocking the mTORC pathway significantly reduced the post-stroke lesion size by decreasing CNS neuroinflammatory responses via a shift in microglial phenotype from M1 to M2 (Li et al. 2016). In spite of the lack of AD-related studies, the data above are suggestive of a promising neuroprotective property of mTOR-signalling inhibitors in AD, via regulation of microglial polarization.

Rho/Rho kinase (ROCK)-pathway inhibitors

Belonging to the Ras superfamily of small GTP binding proteins, Rho provides an important regulatory function in cellular migration and proliferation. Rho-associated protein kinase (ROCK), a member of the AGC (PKA/PKG/PKC) family of serine–threonine kinases, is a downstream effector protein of the small GTPase Rho (Knaus 2000). Being widely distributed in immune-related cells such as

T cells, B cells and NK cells, the ROCK-signalling pathway potently promotes infectious and immune inflammation (Wei and Jun-Qi 2017). Furthermore, more and more studies have shown that ROCK inhibitors exert positive regulatory effects on microglial polarization in neurodegenerative diseases. Roser et al. (2017) found that Rho/ROCK-pathway inhibitors could induce the shift from M1 to M2 microglial phenotype, which has become a promising treatment option for Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS). Zhao et al. (2015) also reported that fasudil, a selective ROCK inhibitor, could prevent MPTP-induced degeneration of dopaminergic neurons. Additionally, fasudil has been shown to convert inflammatory M1 microglia to anti-inflammatory M2 microglia in an MPTP-mouse model of PD. Similarly, in mouse BV-2 microglia, treatment with fasudil regulated microglia polarization towards the beneficial M2 phenotype. In experimental autoimmune encephalomyelitis (EAE) mice, both CD11b(+)ins(+) and CD11b(+) TNF-α(+) M1 microglia were significantly decreased, whereas CD11b(+)IL-10(+) M2 microglia were increased by fasudil administration, which resulted in the amelioration of demyelination and neuroinflammation (Chen et al. 2014). Additionally, the novel ROCK inhibitor, WAR-5 (which is a Y-27632 derivative), protected against myelin impairment and neuroinflammatory injury in EAE C57BL/6 mice, via promoting the M1-to-M2 microglial transition (Li et al. 2015). In a model of traumatic SCI, blocking the Rho/ROCK pathway promoted a shift from M1 microglia/macrophages towards the M2 phenotype, and alleviated CNS inflammatory damage (Dyck et al. 2018). Additionally, inhibition of the Rho/Rho kinase by the prostaglandin E2 receptor EP3 reduced thrombin-induced brain injury, neurologic deficits and numbers of CD68(+) microglia, whereas it increased the number of Ym-1(+) M2 microglia (Han et al. 2015). Another study investigated the link between ROCK signalling and microglial polarization in an AD transgenic model. Yu et al. (2017) found that fasudil improved spatial cognitive impairment in APP/PS1 mice by facilitating the M1-to-M2 microglial transformation. Taken together, ROCK-pathway inhibitors may mitigate AD pathology by modulating microglial phenotypes.

NF-κB pathway inhibitors

Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) is a protein complex that is implicated in cytokine production, cellular survival and synaptic plasticity in response to external stimuli such as infection, stress and free radicals. Besides, NF-κB is a major transcription factor that modulates genes responsible for both the innate and adaptive immune responses (Smith et al. 2006). Many studies have revealed that NF-κB signalling is involved in AD-associated neuroinflammation. Moreover, NF-κB pathway blockage alleviates inflammatory responses and pathological damage in AD models (Kim et al. 2017; Spagnuolo et al. 2018; Zhao et al. 2018). The NF-κB pathway also plays a crucial role in microglial polarization in AD. In vitro, tianeptine treatment has been shown to attenuate neuroinflammation and promote the transition of M1 towards the M2 microglial phenotype in lipopolysaccharide-stimulated cultures via suppression of both the NLRP3 inflammasome and TLR4/NF-κB signalling (Ślusarczyk et al. 2018). Another study found that silencing TRAM1 effectively inhibited LPS/IFN-γ-induced neuroinflammation by M1 microglia in BV2 cells. Moreover, TRAM1 is also essential for phosphorylation of IκB and P65-NF-kB translocation to the nucleus (Wang et al. 2016). In vivo studies have also confirmed the relationship between NF-κB signalling and microglial polarization. In a rat model of neuropathy via chronic-constriction injury to the sciatic nerve (CCI), M1-mediated cytokines (IL-1β, IL-18, and iNOS) were reduced by parthenolide (PTL) treatment, and M2 (IL-10, TIMP1) factors were enhanced. In addition, PTL downregulated the phosphorylated form of NF-κB, p38MAPK, and ERK1/2 protein levels (Popiolekbarczyk et al. 2015). Zhang et al. found that acute hypoxia upregulated M1 microglial markers (e.g., differentiation 86 [CD86]) and downregulated M2 markers (e.g., Arg-1, CD206, IL-4 and IL-10) in both APPswe/PS1dE9 transgenic (Tg) and wild type (Wt) mice. The effects were associated with NF-κB induction through the toll-like receptor 4 (TLR4) (Zhang et al. 2017). Our previous study demonstrated that M1/M2 microglial phenotypes could be modulated by aging via TLR2/NF-κB signalling in MPTP-PD mice (Yao and Zhao 2018). Wang et al. (2015b) also found that tanshinone I administration markedly increased anti-inflammatory M2 gene expression and reduced pro-inflammatory M1 gene expression in LPS-induced BV-2 microglial cells and MPTP-PD mice via inhibiting NF-κB activation. In a murine model of experimental autoimmune uveitis, silencing aryl hydrocarbon receptor (AhR) led to significantly increased macrophage/microglia cells and transition from the M2 to the M1 phenotype as compared to that of AhR+/+EAU mice. Moreover, this result was associated with the activation of NF-κB and signalling transducers and activators of transcriptional (STAT) pathways. Furthermore, AhR-agonist treatment could prevent macrophage/microglia activation, and shifted their polarization from M1 to M2 (Huang et al. 2018). The precise modulation of microglial polarization by the NF-κB pathway requires further investigation in AD models.

NOTCH-signalling inhibitors

As a highly conserved signalling system in most multicellular organisms (Artavanistsakonas et al. 1999), the Notch-signalling pathway is involved in multiple cellular

Table 1 Details of studies about neuroprotective therapy targeting microglia polarization in vitro

Drug/agent	Concentration	Mechanism	References	Effects
Betulinic acid (BA)	10 mM	AMPK-signalling agonist PPARy	Li et al. (2018)	Promoted M2 polarization and inhibited M1 polarization in LPS-stimulated BV-2 microglial cells
T0070907	10 μM	PPARy agonist, AMPK-signalling agonist	Ji et al. (2018)	Increased the expression of M2 markers, including CD206 and IL-4, and reduced the expression of Ml markers, such as CD86, Cox-2 in primary microglia
Telmisartan	10 Mμ	Angiotensin II type 1 receptor blockers/AMPK-signalling agonist	Xu et al. (2015)	Suppressed glutamate-induced inflammation in cultured primary neurons, promoted M1 to M2 polarization transition in LPS-stimulated BV2 and primary microglia cells
5-Amino-4-imidazole carboxamide riboside (AICAR)	1 mM	AMPK-signalling agonist	Giri et al. (2004)	Inhibited LPS-induced expression of pro-inflammatory cytokines (TNF, IL-l , and IL-6) and i-NOS in primary rat astrocytes, microglia, and peritoneal macrophages
Pioglitazone	10 μM	PPARγ agonist	Zhao et al. (2016)	Reversed the imbalance of M1 and M2 inflammatory cytokines in LPS-stimulated N9 microglial cells
DSP-8658	3 μM	PPAR α/γ agonist	Yamanaka et al. (2012)	Promoted A clearance by microglial in rat primary microglia exposure to A
miR-124-3p-up-regulated exosomes (I+EX0-124)	3×10^8	mTOR signalling inhibitor	Huang et al. (2017)	Promoted the anti-inflamed M2 polarization in microglia, inhibited neuronal inflammation in scratch-injured neurons
Salidroside	200 μM	mTOR signalling inhibitor	Wang et al. (2017)	Prevented apoptosis of PC12 cells in coculture with LPS-induced BV-2 microglia, also suppressed Ml polarization in BV-2 microglia
Simvastatin	20 g/ml	Notch-signalling inhibitor	Wu et al. (2017)	M1 markers increase by LPS and Jagged-1 was attenuated, and LPS-treated M2 markers were enhanced in BV-2 cells
y-Secretase inhibitor (GSI)	75 μM	Notch-signalling inhibitor	Liu et al. (2012a, b)	Suppressed the Ml polarization, promoted the M2 polarization in LPS-stimulated N9 microglia
Tianeptine	10 μM	Toll-like receptor 4 (TLR4)/NF-KB pathway blockage	Slusarczyk et al. (2018)	Inhibited M1 polarization and attenuated the production of inflammatory mediators in LPS-stimulated primary microglial cells
Fasudil	15 μg/mL	Rho kinase (ROCK) pathway inhibitor	Chen et al. (2014)	Inhibited the proliferation of antigen-reactive T cells and IL-17-expressing CD4+ T cells, up-regulated CD4+CD25 high and CD4+IL-1o+ regulatory T cells (Tregs) and IL-10 production in BV-2 microglia
Scriptaid	1 μM	Class I/II histone deacetylases (HDACs) inhibitor	Wang et al. (2015a)	Polarized microglia toward M2 in primary co-cultures of microglia and oligodendrocytes, associated with increased preservation of neighbouring oligodendrocytes

Table 1 (continued)

Drug/agent	Concentration	Mechanism	References	Effects
TGF-Fh	2 ng/ml	Smad3 signalling activator	Tichauer and von Bernhardi (2012)	Increased clearance of and reduced activation of microglia through nitric oxide (NO) induced by LPS in microglial cell cultures
SP600125	0.5–5 μM	Inhibitor of JNKs	Waetzig et al. (2005)	Reduced the LPS-induced upregulation of Cox-2, TNF-a, MCP-1 and IL-6 in microglia cells
Exenatide	10 nM	p38MAPK signalling agonists	Wu et al. (2017)	Stimulated the expression of M2 markers such as Arg 1, CD206 and IL-4 in cultured primary microglial cells
T lymphocytes (Tregs)	–	GSK3 signalling inhibitor	Zhou et al. (2016)	Changed the polarization of microglia, decreased the expression of MHC-TT, IL-6, and TNF-a and increased CD206 expression in a transwell co-culture model of microglia and Tregs

differentiation processes during embryonic and adult life, such as neuronal development (Bolós et al. 2007) and angiogenesis (Liu et al. 2003). Notch signalling has also been reported to participate in inflammatory and immune processes (Dimitris and Nussenzweig 2007). Recent studies have demonstrated that Notch signalling could modulate polarization of macrophages/microglia in the CNS. Wu et al. (2017) found that the simvastatin and Notch-signalling inhibitor DAPT could enhance M2 microglia polarization and reduce M1-marker expression in LPS-treated BV-2 cells. A study using morphometric and phenotypic analyses of microglial cells found that arginase-1(+) cells were markedly increased in mice induced by pituitary-adenylate cyclase-activating polypeptide (PACAP)-expressing cells. Additionally, some key transcriptional factors (e.g., Notch/RBP-J) are potential targets of PACAP (Brifault et al. 2015). Liu et al. (2012a, b) found that Notch signalling was related to microglial polarization. Also, Notch-signalling blockage resulted in suppressed M1 polarization and increased M2 polarization. Another study showed that primary microglial cells treated with ol-Aβ and f-Aβ expressed high levels of M1 markers (e.g., IL-1β, IL-6, TNF-α, NOS-II, COX-2), whereas the M2 microglial marker, arginase1, was downregulated. Hes-1, a target molecule of the Notch pathway, was also decreased (Michelucci 2009). The data above indicate that Notch signalling is importantly involved in Aβ-induced microglial polarization and neuroinflammatory responses. Hence, Notch-pathway inhibitors deserve more attention in AD-related investigations.

GSK3-signalling inhibitors

GSK-3β, a serine/threonine kinase, is considered to affect cellular proliferation and inflammation. GSK-3β also aggravates tau phosphorylation, Aβ deposition and promotes progression of AD (Maqbool and Hoda 2017). A selective GSK-3 peptide-derivative inhibitor exhibited neuroprotective properties via alleviating Aβ levels and inflammatory injury in a transgenic AD mouse model (Licht-Murava et al. 2016). Previous studies have reported that the GSK-3β signalling pathway is closely related to CNS microglial polarization. Jiang et al. (2018) found that overexpression of TREM2 could prevent pro-inflammatory cytokines, such as IL-1β, via inhibiting the activity of GSK-3β. Increased Arg1 expression and improved behaviour were also observed in the transgenic mice following TREM2 overexpression. Another study used a lentiviral-mediated strategy to selectively overexpress TREM2 in microglia in the brains of P301S tau-transgenic mice. The study showed that TREM2 overexpression significantly suppressed neuroinflammation by promoting M2 microglia generation, which consequently ameliorated neuronal/synaptic loss, tau hyperphosphorylation and cognitive deficits. The protective effect was due

Table 2 Details of studies about neuroprotective therapy targeting microglia polarization in vitro

Drug/agent	Concentration	Mechanism	References	Effects
Betulinic acid (BA)	2.5 mg/kg/day, intragastrically, for 3 weeks	AMPK-signalling agonist	Li et al. (2018)	Promoted M2 microglial polarization in the cerebral cortex of LPS-injected mice brains
5-Amino-4-imidazole carboxamide riboside (AICAR)	100 mg/kg, i.p., 30 min before LPS treatment	AMPK-signalling agonist	Giri et al. (2004)	Inhibited inflammatory response in LPS-injected rats' brains
Pioglitazone	2.5 mg/kg/day, intragastrically, for 3 weeks	Proliferator-activated receptor-y(PPARy) agonist	Zhao et al. (2016)	Ameliorated depression-like behaviours, inhibited the numbers of microglia, promoted Ml to M2 microglial phenotype transition in chronic mild stress (CMS)-treated mice
Pioglitazone	80 mg/kg/day, gavaged for 9 days	PPARy agonist	Mandrekarcolucci et al. (2012)	Reduced AP level, polarized microglia from M1 into M2 in APPswe/PS1 e9 mice brains
DSP-8658	Daily food intake x 1000 × 0.1%/100/mean body weight (mg/kg/day), for 3 months	PPAR α/γ agonist	Yamanaka et al. (2012)	Enhanced the microglial uptake of Ap, reduced cortical and hippocampal Ap level, improved spatial memory performance in (APP/PS1) transgenic mice
Rosiglitazone	5 mg/kg/day, intragastrically, for 4 weeks	PPARg agonist	Escribano et al. (2010)	Reduced AP burden and inflammatory response, switched the activated microglial phenotype in the hippocampus and entorhinal cortex of AD transgenic mice
Fasudil	25 mg/kg/day, i.p., for 2 months	Rho kinase (ROCK) pathway inhibitor	Yu et al. (2017)	Improved cognitive impairment, decreased the expressions of AP t-42 and iNOS and increased ARG1/CD206 in the hippocampus and cerebral cortex of APP/PS1 transgenic mice
WAR-S	40 mg/kg/day, i.p., on day 3 post-immunization (p.i.) till day 27 p.i.	ROCK-pathway inhibitor	Li et al. (2015)	Alleviated the clinical symptoms, myelin damage and reduced CNS inflammatory responses; converted M1 toward M2 microglia/macrophages in experimental autoimmune encephalomyelitis (EAE) mice
Prostaglandin EP3 receptor (EP3R) antagonist AE240	3 mg/kg, i.p., at 20 min and 6 h after striatal thrombin injection and then twice daily for up to 72 h	ROCK-pathway inhibitor	Han et al. (2015)	Reduced lesion volume, neurologic deficit, and the number of CD68+ microglia, increased the number of Ym-1 + M2 microglia in thrombin-induced brain injury mice

Table 2 (continued)

Drug/agent	Concentration	Mechanism	References	Effects
Fasudil	40 mg/kg/day, i.p., from day 3 to day 27 pi	ROCK-pathway inhibitor	Chen et al. (2014)	Decreased both CD11b+iNos+ and CD11b+TNF-a+ M1 microglia, and increased CD11b+IL-10+ M2 microglia in experimental autoimmune encephalomyelitis (EAE) mice
Paeoniforin (PF)	40 mg/kg/day, intraperitoneally, for 27 days	Cannabinoid receptor 2 (CB2R) agonist, mTORINF-KB inhibitor	Luo et al. (2018)	Attenuated cognitive impairment, promoted an M1 to M2 transition in microglia/macrophage in the hippocampal of permanent four-vessel occlusion rat model
miR-124-3p-up-regulated microglial exosomes	Administered intravenously via tail vein (30 mg total protein of exosome/mice) at 1 h after the first time of injury	mTOR signalling inhibitor	Huang et al. (2017)	Improved the neurologic outcome and inhibited neuroinflammation in mice with traumatic brain injury
Salidroside	25 mg/kg/d, i . p.	mTOR signalling inhibitor	Wang et al. (2017)	Improved the functional recovery, suppressed M1 microglia polarization and activated M2 microglia polarization in rats after Spinal cord injury (SCI)
ILP and lSP	10 μg/day, intrathecally	Disruption of LAR and PTPσ	Dyck et al. (2018)	Shifted M1 microglia-macrophages towards alternative M2 phenotype, and alleviated CNS inflammatory damage in traumatic spinal cord injury (SCI) rats
AAV-TREM2 (adeno-associated viral (AAV) vector encoding TREM2)	1 μl (2.08×10^{15} TU/μ1), intracerebroventricular injection	GSK3 signalling inhibitor	Jiang et al. (2018)	Improved surgery-induced cognitive deficits and neuroinflammatory responses, increased Arg1 expression in APPswe/PS1dE9 mice brains
CD28 super-agonist antibody (clone D665)	50 μg, i.p., 3 h after ICH	GSK3 signalling inhibitor	Zhou et al. (2016)	Reduced the inflammatory injury, shifted microglia/macrophage polarization from M1 to M2 phenotype in intracerebral haemorrhage (ICH) mice model
L807mts	60 mg per dose, nasally, for 120 days	GSK3 signalling inhibitor	Licht-Murava et al. (2016)	Enhanced the clearance of P-amyloid loads, reduced inflammation, enhanced autophagic flux, and improved cognitive and social skills in the 5XFAD AD mouse model

Table 2 (continued)

Drug/agent	Concentration	Mechanism	References	Effects
Parthenolide (PTL)	5 μg, intrathecal (i.t.) injection	NF-KB pathway blockage	Popiolekbarczyk et al. (2015)	Reduced the protein level of M1 (IL-1p, IL-18, and iNOS) and enhanced M2 (IL-10, TIMP1) factors in chronic-constriction injury to the sciatic nerve (CCI)-induced neuropathy in rat
Physical exercise	–	ERK and JNK signalling activator	Jiang et al. (2017)	Improved the cognitive function, alleviated myel in injury, triggered oligodendrocyte progenitor cells (OPCs) proliferation and differentiation, facilitated microglia polarization toward M2 in rats with chronic cerebral hypoperfusion (CCH)
SP600125	30 mg/kg/day, for 12 weeks	JNK signalling inhibitor	Zhou et al. (2015)	Promoted non-amyloidogenic APP processing and inhibited amyloidogenic APP processing, reduced neuroinflammation in the APPswe/PS1dE9 mice
Sildenafil	10 mg/kg/day, i.p., for 7 days	Phosphodiesterase-5(PDE5) inhibitors	Zhang et al. (2013)	Reversed memory deficits, reduced AP level, decreased the mRNA levels of TL-1 p and TNF-a in the hippocampus of APP/PS1 m ice
Glatiramer acetate	s.c. injected five times with a total of 100 g	IGF-1 signalling activator	Butovsky et al. (2006)	Decreased plaque formation, reduced cognitive decline, switched microglial phenotype to dendritic-like (CDl lc) cells in APP/PS1 mice brains
Scriptaid	3.5 mg/kg, i.p., at 2, 26, and 50 h after CCI	Class I/II histone deacetylases (HDACs) inhibitor	Wang et al. (2015a)	Protected white matter, improved nerve conduction, shifted microglia/macrophage polarization toward M2 phenotype and mitigated inflammation in severe traumatic brain injury (TBT) models brains
AAV-IL-4 (adeno-associated viral (AAV) vector encoding IL-4)	2×10^9 VP, stereotactic injected into mouse hippocampus	*N*-Methyl-D-aspartate (NMDA) receptor agonist	Kiyota et al. (2010)	Improved spatial learning, reduced astro/microgliosis, amyloid-beta peptide oligomerization and deposition, and enhanced neurogenesis in APP/PSl mice
sRAGE-MSCsl11	5 μL, stereotactic injected into the entorhinal cortex (ENT)	RAGE signalling inhibitor	Oh et al. (2017)	Reduced CD4 and CD3d-positive T lymphocyte and M1 microglia numbers, increased M2 microglia numbers, prevented neuron decrease in Ap1–42 treated rat brains

Table 2 (continued)

Drug/agent	Concentration	Mechanism	References	Effects
Deferoxamine	10 mg/ml, i.p, twice a day, for 7 d ays	Antiapoptotic agent	Zhang et al. (2017)	Ameliorated cognitive function and deposition of Ap, induced M2 activation of microglia and inhibited MI activation of microglia in the hippocampus of APP/PS1 mice

sRAGE a soluble form of receptor for advanced glycation end-products secreting mesenchymal stem cells, *LAR* leukocyte common antigen-related, *PTPσ* protein tyrosine phosphatase-sigma

to the inhibition of GSK3β and cyclin-dependent kinase 5 (CDK5) (Jiang et al. 2016). In a model of traumatic brain injury (TBI), the class I/II histone deacetylase (HDAC) inhibitor, scriptaid, could shift microglia/macrophage polarization from the M1-to-M2 phenotype and mitigate inflammatory responses via GSK3β/PTEN/Akt signalling. Moreover, scriptaid significantly increased myelin-basic protein expression and improved neuronal function (Wang et al. 2015a). Zhou et al. (2016) found that regulatory T lymphocytes (Tregs) alleviated intracerebral haemorrhage (ICH)-induced inflammatory injury by modulating microglia/macrophage polarization toward the M2 phenotype through the IL-10/GSK3β/PTEN axis. The data above suggest that GSK3 blockage may inhibit neuroinflammatory damage by regulating microglial polarization in several disease models, which deserves further investigation in AD-related models (Tables 1, 2).

Other signalling pathways

Some other signalling pathways also play an important role in the regulation of microglial polarization. A recent study investigated the effects of the brain renin–angiotensin system (RAS) on microglial polarization. Angiotensin II (Ang II) exerts pro-oxidative and pro-inflammatory effects via its type-1 receptor (AT1). However, Ang II/AT2 receptor signalling and Angiotensin 1-7/Mas receptor (MasR) signalling provide anti-inflammatory functions and promote M2 polarization, which has the prospect of becoming a novel therapeutic approach in AD (Labandeiragarcia et al. 2017). Oh et al. injected sRAGE-secreting mesenchymal stem cells (sRAGE-MSCs), along with Aβ1-42, into the entorhinal cortices of male Sprague–Dawley rats. The results showed that sRAGE-MSCs significantly downregulated RAGE and RAGE- ligand expressions; simultaneously, the number of M2 microglia increased and the number of M1 microglia decreased. Consequently, sRAGE-MSC transplantation provided a neuroprotective effect in Aβ1-42-treated rat brains. These observations suggest that RAGE signalling is involved in microglial polarization in AD (Oh et al. 2017). Glatiramer acetate (GA) is commonly used in the treatment of multiple sclerosis, and has been reported to alter the inflammatory environment by upregulating IL-4 and recruiting Th2 T cells to the CNS. GA administration accelerates Aβ clearance and switches microglial phenotypes, similar to those of treatments with IL-4, by activating IGF-1 signalling (Butovsky et al. 2006; 2007). This study indicated the potential regulatory effect of IGF-1 signalling in microglial polarization in AD. Cytokines also exert crucial effects in microglial-phenotypic modulation. Interleukin-4, the prototypic M2-inducing cytokine, reduces Aβ production and improves cognitive ability in an AD model (Kiyota et al. 2010). Furthermore, as a potent anti-inflammatory cytokine,

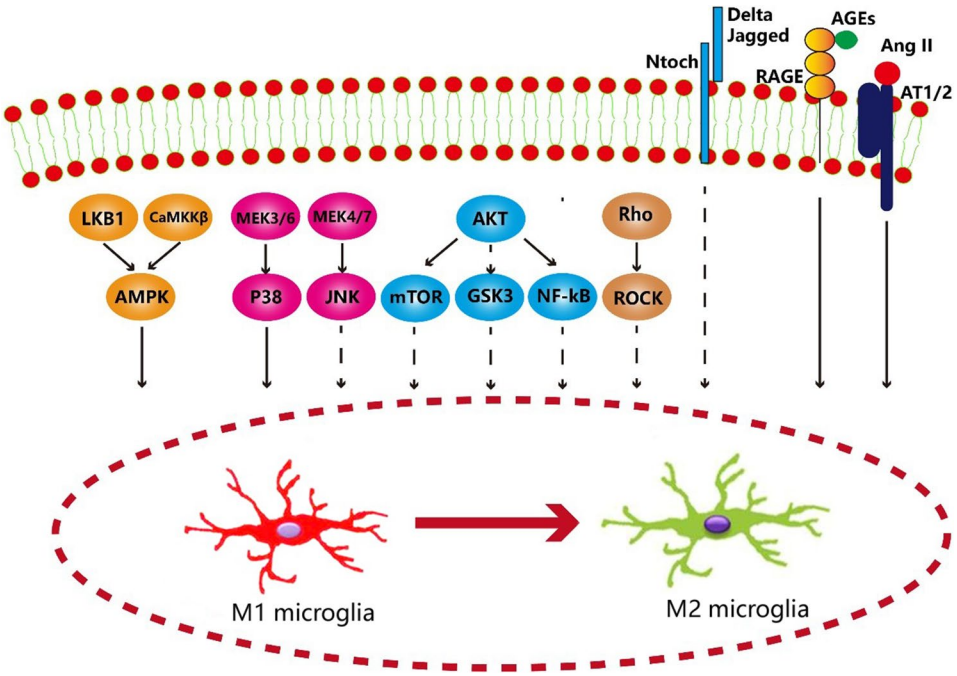

Fig. 1 The therapeutic targeted signalling pathway involved in the microglia polarization in Alzheimer's disease (AD). Activation is represented by solid lines; inhibition is represented by dashed lines

TGF-β polarizes microglia to the M2c phenotype, which consequently enhances microglial uptake of Aβ (Tichauer and von Bernhardi 2012) and alleviates AD-related pathology (Wyss-Coray et al. 2001; Tesseur et al. 2006). Interestingly, another in vivo study reported that deferoxamine enhanced alternative M2 microglial activation and inhibited Aβ deposits in 12-month-old APP/PS1 mice. This result indicated the potential interaction between iron metabolism and microglial polarization in AD (Zhang and He 2017). Among the MAPKs, JNK is one of the most important microglial inflammatory modulators (Waetzig et al. 2005). In vivo treatment of the JNK inhibitor, SP600125, markedly reduced Aβ production, neuroinflammatory responses, synaptic loss and cognitive impairment in a transgenic AD mouse model (Zhou et al. 2015). In rats with CCH, Jiang et al. (2017) found that physical exercise improved cognitive function, alleviated myelin injury, shifted microglia polarization to M2 and reduced ERK and JNK phosphorylation. In cultured primary microglial cells, treatment with exenatide, a GLP-1 receptor agonist, stimulated the expression of M2 markers (e.g., Arg 1, CD206 and IL-4). The effect was blocked by the p38 MAPK inhibitor, SB203580, and the gene silencer, siRNA/p38β, indicating that p38/MAPK signalling is strongly associated with exenatide-induced microglial polarization (Wu et al. 2018) (Fig. 1).

Conclusions

Microglia-mediated neuroinflammation plays a crucial role in the onset and development of AD. During the procession of AD, the dysfunction of M2 microglia and the excessive activation of M1 microglia promote inflammatory injury and pathological damage. Furthermore, many studies have demonstrated that modulation of microglial polarization from the M1 to the M2 phenotype ameliorates neuroinflammatory responses, Aβ deposits and tau hyperphosphorylation in AD. Hence, modulation of microglial phenotypes may represent a promising therapeutic approach for the treatment of AD. Importantly, several signalling pathways—such as AMPK, mTOR, ROCK, NF-κB, NOTCH and GSK3—may be critically involved in microglial polarization in AD. However, the underlying mechanisms of microglial polarization in AD are still not well understood, and future experiments are required for their further elucidations.

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Author contributions KY was responsible for the design and manuscript drafting. HZ contributed to figure generation and manuscript writing. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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